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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,263	05/25/2006	Sui Xiong Cai	1735.0940001/RWE/BSA	2574

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EXAMINER	
COPPINS, JANET L	

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,263	CAI ET AL.	
	Examiner	Art Unit	
	JANET L. COPPINS	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18-20* is/are allowed.

6)☒ Claim(s) *1-17 and 21* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22 are currently pending in the instant application.

Priority

2. The instant application is a 371 of PCT/US2004/042292, filed December 17, 2004.

Information Disclosure Statement

3. Applicants' Information Disclosure Statement (IDS), submitted July 19, 2007, has been considered by the Examiner. Please refer to the signed copy of Applicants' PTO-1449 form, submitted herewith.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-17 rejected under 35 U.S.C. 112, first paragraph, as not being fully enabled. While the various diseases/disorders may be listed on page 13 of the specification, the claims are not enabled for treating or preventing *all* conditions or diseases "responsive to the induction of apoptosis", since there is no indication as to the full range of diseases or cancers that could be treated using the instant claimed process.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,

6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, the claims are directed to treating or preventing many diseases and conditions that are not enabled in the specification, including those broadly recited in claim 1; as well as the cancer(s) recited in claims 3-6, 8 and 9; autoimmune diseases of claim 10; infectious viral diseases of claim 11; inflammatory disease of claim 13; and skin disease of claim 15.

The nature of the invention

The nature of the invention is of methods of treating or preventing many different diseases or conditions that respond to the induction of apoptosis, including cancer, autoimmune disease, infectious viral disease, inflammatory disease, and skin disease, comprising administering the instant claimed gambogate compounds to a patient in need thereof.

The state of the prior art and the predictability or lack thereof in the art

It is well recognized in the medical art that treatment of diseases or symptoms are not analogous terms. Furthermore, the diseases listed on page 13 of the Specification, as well as those encompassed by claim and autoimmune disease of claim 10, and infectious viral disease of claim 11, are not the same but include many different unrelated and extremely complex diseases/conditions including cancer, diabetes, neurodegenerative diseases, psoriasis, Lupus, HIV, hepatitis, etc. The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

This unpredictability is more pronounced where the diseases disclosed in the

Specification are as complex and diverse in etiology and patient populations as the many different types disclosed in this application. Even though gambogic acid compounds have been identified as having antiproliferative activity, as a practical matter their use as therapeutic agents for treating or preventing cancer, or for treating a broad range of types of cancer, remains highly unpredictable. As to "preventing" such diseases as cancer by use of gambogic acid compounds, the examiner was not able to locate prospective clinical studies in the art demonstrating blanket "prevention" of cancer, so there were no benchmarks against which to compare the efficacy of the claimed compounds for the absolute prevention of cancer, had the Specification done so. In light of the highly unpredictable nature of this art, the Specification failed to disclose facts which would enable the skilled artisan to use the recited gambogate compounds to prevent cancer without undue experimentation.

On the other hand, use of the claimed gambogate compounds to "treat" certain specific types of cancerous cell lines, such as clinical studies of patients with cancerous tumors, that are already known and published in the art, greatly reducing the unpredictability for "treating" those types of cancer, or for "inhibiting the growth of" those types of cancerous tumors, would be permissable.

Also, in the absence of a showing of correlation between **all of** the diseases claimed (i.e. autoimmune, infectious viral diseases, inflammatory diseases, etc) as capable of being treated by the gambogate compounds of claim 1 and the response of induction of apoptosis, one of skill in the art is unable to fully predict possible results from the administration of the compounds of claim 1.

The amount of direction or guidance present

The specification has enabled only the gambogate compounds according to claim 1 that selectively induce apoptosis *in vitro*. There appeared to be no working examples provided in the Specification where a gambogic acid compound was administered to a mammal for treating or preventing a disorder of any kind. Treatment of the claimed broad range of diseases are normally disease or symptom oriented, thus are highly individualized, i.e. treating each and every disorder encompassed by the claimed "disorder responsive to the induction of apoptosis" would not employ the same methods. The efficacy of an individual compound against a specific disease or symptom needs to be specifically and individually supported by factual evidence. Such evidence has not been described or supported by the specification.

The presence or absence of working examples

The data provided in the disclosure is insufficient evidence for methods of treating or preventing the claimed conditions or diseases. In fact, the only disclosure in the specification at all is found on pages 41-44 wherein two *in vitro* binding assays are described, wherein displacement of a radiolabeled test ligand from human breast cancer cell lines is measured. Applicant provides **no** working examples which support the claim to a treatment of any specific disease or disorder. Rather, Applicant provides *in vitro* antiproliferative data. Those of skill in the art recognize that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking.

The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single

extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that many differences exist between cultured cells and their counterparts *in vivo*.

These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This result has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro).

Further, with respect to the treatment of cancer, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in

the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Applicants have provided evidence that the compounds are effective for inhibiting cell proliferation within single certain cancer cell lines, however "the selection of the examples… used as the disclosure to support a claim must be adequately representative of the area covered by it," please see *In re Cavallito et al.* (CCPA 1970) 429 F2d 452, 166 USPQ 552. Therefore the instant specification is lacking significant data to accommodate as many diseases or conditions as the claims are alleging by broadly reciting, "A method for treating, preventing or ameliorating a disorder responsive to the induction of apoptosis," including all cancers of claims 3-6, 8 and 9; autoimmune disease of claim 10; infectious viral disease of claim 11; inflammatory disease of claim 13; and skin disease of claim 15.

The breadth of the claims

Applicants are claiming methods of treating an extremely broad number of complex diseases or conditions, for which the majority have no known successful treatment or cure. The argument that the diseases claimed by the Applicants are all treated by inducing apoptosis is insufficient support that the claimed compounds have specific efficacy in current available form for treating or preventing all of the diseases and conditions encompassed by the language of claim 1.

Claim 10 recites treating autoimmune disease, which refers to diseases against "self," and includes such diverse and varied diseases as rheumatoid arthritis, scleroderma, lupus erythematosus, Crohn's diseases, ulcerative colitis, etc. Treating autoimmune diseases employs

the use of immunosupressants, however the state of the art does not teach one compound for the absolute treatment or prevention of *any* or *all* of these diseases. Furthermore, the etiological causes of many of the claimed disorders, including neurodegenerative disorders are unknown. While symptomatic treatments are available for many of these disorders, drugs to reduce or prevent the progression of the disease in patients have yet to be identified.

Claim 11 recites treating "infectious viral diseases," which includes such difficult and diverse viral infections to be treated such as Adenoviruses, Enteroviruses, Rhinoviruses, Influenza, Rubella, Epstein-Barr, mononucleosis, herpesviruses, Cytomegalovirus, HIV and AIDS. Furthermore, autoimmune diseases can take several different forms and their exact cause remains unknown, treatment has been extremely difficult and there are currently no successful treatments or cures.

The scope of claims 3-6, 8 and 9 reasonably encompasses such a broad spectrum of types of cancer that it is unreasonable to believe, on its face, that any particular chemical compound could be used treating or preventing cancer or "drug resistant cancer" or the laundry list of cancers recited in claim 4, encompassing so many different types, in the absence of supporting scientific data or references in the disclosure to the contrary. Due to the unpredictable nature of cancer and the fact that over 3,000 different cancers exist, the various types of cancers have different causative agents, involve different cellular mechanisms, and differ in treatment protocol, thus no single compound exists presently that is known to treat *all* cancers as a blanket therapeutic. Furthermore, the Merck® manual currently has many cancer treating agents (over 12,000 compounds), yet they are only known to treat a few cancers each.

Treating "inflammatory disease" of claim 13 encompasses treating hundreds of thousands

of possible unrelated diseases and conditions, which can affect nearly every system in the human body, including asthma, autoimmune disease, chronic inflammation, inflammatory bowel diseases, pelvic inflammatory disease, reperfusion injury, rheumatoid arthritis, transplant rejection, and vasculitis, for example. Currently no therapeutic compound is known to be effective for treating the broad range of all "inflammatory disease(s)."

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art, without direction, would be unable to treat or prevent each and every disease/condition encompassed by claim 1 using the instant claimed gambogate compounds. One of skill in the art would need to determine which of the thousands of diseases encompassed by claim 1 would be benefited by the inducing apoptosis and would furthermore then have to determine whether the claimed compounds would provide treatment of all of the diseases and conditions by said activity.

The level of the skill in the art

Those practitioners who treat proliferative diseases or cancer of any type (medical clinicians, pharmacists and/or pharmaceutical chemists) presumably would be highly skilled in the art.

However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the treatment of <u>all</u> claimed diseases/conditions in claim 11. As a

result, necessitating one of skill to perform an exhaustive search for which claimed diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

There is no question Applicant's claimed gambogate compounds may play a role in future methods of treating several of the aforementioned diseases/disorders. What is disputed is the claim that the compounds of claim 1 could be taken by a POSITA at the time of filing and used as treatments for the diseases/disorders recited in claims 1-17, without undue experimentation. At the time of filing or even at present, the most which can be said about the claimed gambogate compounds is that certain of the compounds possess the ability to inhibit cell proliferation in *vitro*. Moving from a discovered mechanism of action to a method of treatment requires a fallacious, inductive leap of logic amounting to undue experimentation. There is simply no evidence to be found in the literature suggesting that Applicant's claimed compounds are capable of being used in the manner recited in claims 1-17. In essence, there is no absolute predictability in pharmacology, even with compounds whose properties have been determined, despite the extraordinarily high skill possessed by the ordinary artisan.

Another deficiency necessary for a POSITA to use Applicant's compounds to treat the broadly recited diseases/disorders is dosage. So far, there is very little, if any, information to be gleaned from the literature on the subject of dosage relating gambogate-derivatives to those diseases/disorders sought to be treated or prevented in the instant Application. There does not seem to be enough knowledge in the art to connect the compounds' properties to the actual treatment of the diseases/disorders claimed, in particular, the long list of cancers recited in claim 4, as well as drug-resistant cancer, autoimmune disease, and infectious viral disease. It does seem that certain gambogic acid derivatives capable of inhibiting cell proliferation may provide useful

therapeutic tools in future. Although, at the time of filing, and even at present, a POSITA would not be able to use the invention as claimed to treat or prevent the vast list of disorders encompassed by the language of claims 1-17.

The Examiner suggests narrowing the scope of disorders to be treated in the claims, and deleting the term "preventing" from all claims, as well as deleting claims 3, 6, 8 and 9, and only reciting specific cancerous cell lines that are **enabled by the disclosure** in claim 4. The Examiner also recommends deleting claim 10 and reciting specific infectious viral disease(s) that are also enabled by the disclosure in claim 11; and inserting specific inflammatory and skin diseases to be treated in claims 13 and 14, respectively.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 21 is rejected as being indefinite for reciting "at least one known cancer chemotherapeutic agent," however it is unclear from the claim itself which chemotherapeutic agent Applicants are intending to claim. The Examiner cautions Applicants when amending the claim to insert only specific agents that are enabled by the Specification.

Claim Objections

8. Claim 22 objected to because of the following informalities: the claim appears to have a printing error, three of the compounds listed on line 7 of the claim are unreadable. Appropriate correction is required.

Conclusion

9. In conclusion, claims 1-22 are currently pending. Claims 1-17 and 21 are rejected. Claims 18-20 appear allowable over the prior art. Claim 22 is objected to.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. COPPINS whose telephone number is (571)272-0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Coppins/
Patent Examiner, Art Unit 1626
March 26, 2009

/REI-TSANG SHIAO/
Primary Examiner, Art Unit 1626